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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/139,425	08/25/1998	CHARLES T. ESMON	OMRF-171	5290

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	29

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/139,425	ESMON ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 12/11/02 has been acknowledged.

Claims 1-25 are pending and were examined in this office action.

▷ *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

Applicant's arguments filed 12/111/02 have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action and new grounds of rejection below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-7, 9-10, 13-14, 19, 21-23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession of the claimed invention.**

The scope of the invention as claimed encompasses any and all types of agents that selectively bind to the endothelial protein C receptor (EPCR). At best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR (see spec. pages 4-6 sec.

B). The specification further teaches that only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in vitro (spec. page 14, example-5). Besides anti-EPCR antibody and activated protein C the specification as filed fails to disclose any other agent that selectively binds to the EPCR and selectively translocate to the nucleus of endothelial cells. Furthermore, the specification as filed only teaches biotinlayted-anti-EPCR antibody and poly-L-lysine conjugated anti-EPCR antibody. The specification fails to disclose all conjugates wherein the conjugation has been achieved by all chemical conjugates, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies (see spec. page 8, sec. D). Furthermore the specification fails to disclose any triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the agent as claimed has been defined only by a statement of function that requires the binding to the endothelial protein C receptor (EPCR), which conveyed no distinguishing information about the identity of the claimed agent, such as its relevant structural or physical characteristics. Similarly, chemical conjugates, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies conveyed no distinguishing information about the identity of the claimed substances,

such as its relevant structural or physical characteristics. Similarly, triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any and all genes conveyed no distinguishing information about the identity of the claimed molecules, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use** the invention.

Nature Of Invention:

The invention is drawn to selective delivery of a molecule to the nucleus of an endothelial cell of the large vessels through Endothelial Protein C Receptor (EPC-Receptor) using agents that selectively binds to the EPC-Receptor. The invention falls in the realm of protein and gene bases therapeutics.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses the use of any and all agents that selectively binds to the EPC-Receptor and translocate to the nucleus of endothelial cells. Given the broadest reasonable interpretation the scope of the molecule to be delivered to cells encompasses a molecule with therapeutic characteristic (see claim 12). In addition the scope of invention as claimed encompasses the delivery of the conjugates in-vivo via any and all routes of administration (local and systemic administration). The scope of invention as claimed encompasses the use of any and all conjugates wherein the conjugation has been achieved by all chemical conjugates, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies. In addition the scope of invention as clamed

encompasses the delivery of any triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene.

At best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR (see spec. pages 4-6 sec. B). The specification further teaches that only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in-vitro (spec. page 14, example-5). The specification discloses the selective delivery of streptavidin by using biotin labeled EPCR monoclonal antibodies (spec. page 13-14, example 3-4). In addition the specification only teaches poly-L-lysine conjugated anti-EPCR antibody. Besides anti-EPCR antibody and activated protein C the specification as filed fails to disclose any other agent that selectively binds to the EPCR and selectively translocate to the nucleus of endothelial cells. In addition the specification as filed fails to disclose a single working example that teaches the delivery of the conjugates in-vivo via any and all routes of administration (systemic or local) that results in the delivery of the molecule to the nucleolus of the endothelial cells of any large blood vessel in a subject.

State Of Art And Predictability:

The state of the art at the time of filing teaches that Protein C functions as an anti coagulant when converted to active serine proteases from endothelial cell surface. Besides having affinity for Endothelial Protein C Receptor (EPCR) the Protein C also binds to the Thrombin-TM receptor complex in the endothelial micro-environment. Furthermore, the expression of Endothelial Protein C Receptor (EPCR) is not limited to endothelial cells of aorta but EPCR is also expressed in abundance in heart and placenta. In addition the EPCR expression has also been detected in lung, kidney and pancreas (see Fukudome et al, J Exp Med. 6;187(7):1029-35, 1998). The art at the time of filing further teaches that the Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current

gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case considering the scope of invention that encompasses in-vivo delivery the specification fails to disclose any particular use of triplex forming oligonucleotides, ribozymes and antisense molecules. In addition the specification fails to disclose how one skilled in art would use any protein and/or diagnostic agent delivered into the nucleus of an endothelial cell. In addition, general systemic delivery of a complex that ends up in a pre-selected location in vivo is one of the most difficult obstacles to overcome. The infused particles binds to many cells they encounter in circulation and therefor would be diluted out before reaching their targets (see Anderson WF, page 25 col.2, para.4).

Therefore considering the state of art that teaches the expression of EPCR on variety of tissues the conjugate containing the activated protein C molecules would end up in heart or placenta that abundantly express the EPC-receptor. Furthermore, the use protein C complex would not be of any use since only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in-vitro (spec. page 14, example-5). In addition, the delivery of the conjugate as claimed, via any route of administration would be highly unpredictable, since EPCR is not only expressed in large blood vessels but also expressed on heart and placenta tissuse. Furthermore, the systemic delivery of the conjugate would also leads the interaction with Thrombin-TM receptor complex, and EPCR expressed on heart and placental tissue thus making the conjugate immobilized before reaching to the EPCR expressed on the targeted large blood vessels.

Quantity Of Experimentation Required:

The applicant argues that instant claims do not require the treatment of any disease or disorder *(response, page 2)*. This is found unpersuasive because given the broadest reasonable interpretation the scope of invention as claimed encompasses a method exercised in-vivo (See also MPEP § 2111). Citing Baumgartner et al (Circulation 97:1114, 1998) the applicant argues that the specification when taken in combination of the state of art clearly enables the invention as claimed. However, this is found NOT persuasive because the cited reference does not requires

the method as claimed but only teaches intra-muscular injection of a naked plasmid construct see page 1115, col.1). It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the applicant fails to disclose all agents (other than anti-EPCR-antibody and activated Protein C) that selectively binds to the EPCR. The specification fails to disclose any and all conjugates wherein the conjugation has been achieved by any all methods of chemical conjugation, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies. In addition the specification fails to disclose any triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene. For example, the specification fails to provide any guidance regarding what portion of an RNA molecule would be accessible in-vivo, since effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside the cells. In addition, the efficacy of antisense therapy is further compounded by the fact that base compositions as well as the secondary and tertiary structure of the target nucleotide sequence determines the accessibility of the sequence to an antisense sequence (see Branch TIBS, 23 Feb, 45-50, 1998).

Furthermore, selectively delivering molecules to the nucleus of endothelial cells of a large blood vessel is not considered routine in the art, and without sufficient guidance to a specific therapeutic molecule the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). In addition the word **"treatment"** *means administration or application of remedies to a patient or for a disease or an injury; medicinal or surgical management; therapy. The*

substance or remedy so applied[1]. Considering the scope of therapeutic molecules (as claimed), it is unclear whether the disease would be the result of the loss of a gene product and/or protein or is the result of altered gene product and/or protein function. It is even unclear whether the treatment of the disease in the context would require increase or decrease in the expression of the gene product and/or related protein. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 13-14 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 19 are indefinite because it is unclear what is "*a drug other than nucleic acid*" in this context.

Claim 13 is indefinite because it is unclear what is "*molecule selected from group consisting of a nucleic acids proteins drugs and diagnostic agents to be delivered to a large vessel endothelial cell, wherein the molecule is not diagnostic label*" in this context.

Claim 14 is indefinite because it is unclear what is "recombinant molecule based of the antibody to EPCR" in this context.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 15, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al (US 5225537, 1993) for the same reasons of record as set forth in the office action mailed on 9/11/02.

The applicant argues that protein C fusion protein of Foster is only a fragment of protein C and not full protein and therefore is not within the scope invention as claimed *(response, page11)*.

However, this is found NOT persuasive because Foster clearly teaches construction of a PAP-C fusion protein by using site directed mutagenesis to fuse PAP-I coding sequence with Protein C DNA. PAP-I is an anticoagulant protein (Col.17, example 3-4). The cited art further teaches a hybrid activated protein C comprising at least one lipocortin phospholipid-binding domain joined to a gla-domainless activated protein C (col22 line 11-23). The cited art teaches the coupling of protein C and activated protein C to PAP and lipocortin domains at molecular level. Given the broadest reasonable interpretation the cited art clearly anticipates the fusion protein coupling means as claimed (see MPEP 2111).

Claims 13, 15, 20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al (US 5571786, 1996) for the same reasons of record as set forth in the office action mailed on 9/11/02.

The applicant argues that one could hardly construe thrombin coupled to Sepharose as a molecule to be delivered to a large vessel endothelial cell. The applicant argues that claim as amended recites "nucleic acid, proteins, drugs and diagnostic agents" *(response, pages11-12)*.

However, this is found NOT persuasive because invention as claimed a conjugate formed by requires indirect binding by a positively charged polymer". Eibl clearly teaches a conjugate wherein the Activated Protein C is attached to thrombin coupled to CNBr-Sepharose 4B (col.6, example-3). The cited art teaches the attachment of a protein (thrombin) to activated protein C. The cited art further teaches the attachment of thrombin-activated protein C complex to a polymer (CNBr-Sepharose4B). Thus the cited art clearly anticipate the conjugate as claimed.

Claims 13-15, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Stearns-Kurosawa et al (PNAS 93:10212-10216, 1996).

The cited art teaches a Boitinlated-protein C preparation (page 10213, col.1 para.3). Thus the cited art clearly anticipated the invention as claimed in claims 13, 15, 20 and 22.

In addition the cited art teaches isolation of anti-EPCR monoclonal antibodies from mouse ascities using protein G column. The cited art further teaches a conjugate comprising anti-EPCR monoclonal antibodies conjugated with fluorescein-labeled anti-mouse IgG. Thus the cited art clearly teaches the antibody to EPCR attached to another molecule (see claim 14). Given the broadest reasonable interpretation to term **-diagnostic**[2] (*Serving to identify a particular disease; characteristic), the* fluorescein-labeled anti-mouse IgG is not a diagnostic agent since it is not used to identify a disease characteristic. Thus the invention as claimed is clearly anticipated by the cited prior art of record.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

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